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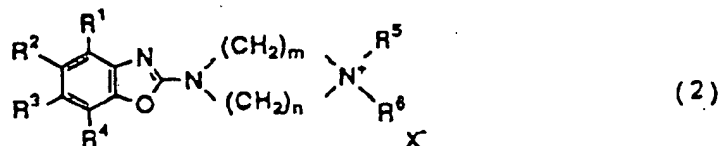
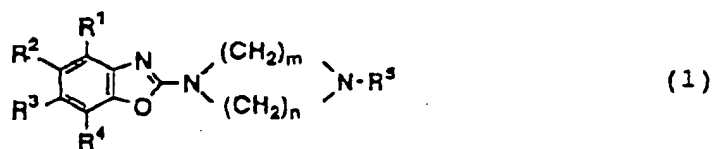
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(54) Benzoxazole derivatives and their use as serotonin 5-HT₃ receptor antagonists.

(57) A benzoxazole derivative of the formula (1) or (2) which has an alicyclic diamine group at the 2-position:

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wherein R^1 , R^2 , R^3 and R^4 may be the same or different and each represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, halogen, hydroxyl, amino, lower alkoxy, carboxyl, carbamoyl and nitro, or any two of R^1 to R^4 may be linked together to form a three to seven-membered ring structure comprising carbon atoms alone or carbon atoms and 1 to 2 hetero atoms, which may be substituted; R^5 and R^6 may be the same or different and each represents substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aralkyl group or an alkoxycarbonyl group, or R^5 and R^6 may be linked together to form a three to seven-membered ring structure comprising carbon atoms and 1 to 2 nitrogen atoms, which may be substituted; X^- is a pharmaceutically acceptable anion; and m and n may be the same or different and each is an integer of 1 to 3. The compound shows excellent 5-HT₃ receptor antagonism and is useful as an antiemetic agent and also as a peristalsis controlling agent, an analgesic agent, an antianxiety agent and a schizophrenia treating agent.

FIELD OF THE INVENTION

This invention relates to benzoxazole derivatives which show serotonin 5-HT₃ receptor antagonism.

5 BACKGROUND OF THE INVENTION

In recent years, compounds having serotonin 5-HT₃ receptor antagonism have been studied extensively and some of them are now used in the clinical field, because of their function to repress nausea and emesis as side effects caused by the use of carcinostatic agents such as cisplatin and the like or by radiotherapy.
10 However, as is evident in benzamide base drugs, these prior art compounds are not always satisfactory in view of their drug effects free from side effects.

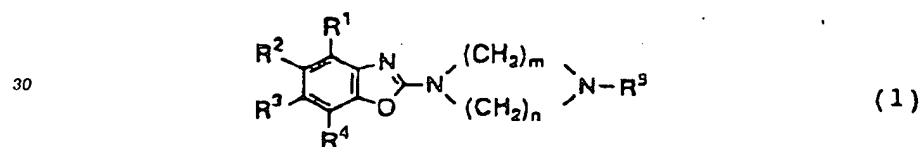
SUMMARY OF THE INVENTION

15 An object of the invention is to provide a compound having an excellent serotonin 5-HT₃ receptor antagonism.

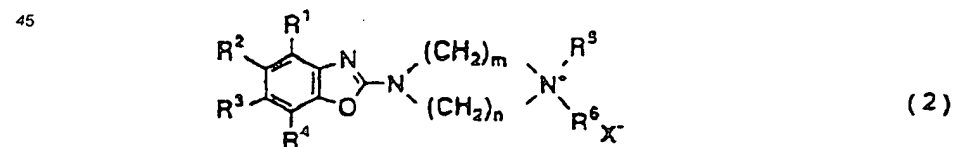
The inventors of the present invention have reported recently that a benzothiazole derivative has an excellent cardiotoxic effect (JP-A-4-316565) (The term "JP-A" as used herein means an "unexamined published Japanese patent application"). Thereafter, the present inventors have continued studies on the
20 synthesis of new derivatives and found that a benzoxazole derivative has a strong and selective 5-HT₃ receptor antagonism.

Since the 5-HT₃ receptor antagonist is possessed of not only antiemetic effect but also peristalsis enhancing effect, analgesic effect, antianxiety effect and the like, it is also useful as a peristalsis controlling agent, an analgesic, an antianxiety agent and an agent for the treatment of schizophrenia.

25 The present invention provides a compound represented by the formula (1)



35 wherein R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a halogen atom, a hydroxyl group, an amino group, a lower alkoxy group, a carboxyl group, a carbamoyl group or a nitro group, in which any two groups of R¹ to R⁴ may be linked to each other to form a three to seven-membered ring structure comprising carbon atoms alone or carbon atoms and 1 to 2 hetero atoms, which
40 may be substituted; R⁵ represents a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted aralkyl group or an alkoxycarbonyl group; and m and n may be the same or different and each is an integer of 1 to 3, and a compound represented by the formula (2)



wherein R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a halogen atom, a hydroxyl group, an amino group, a lower alkoxy group, a carboxyl group, a carbamoyl group or a nitro group, in which any two groups of R¹ to R⁴ may be linked to each other to form a three to seven-membered ring structure comprising carbon atoms alone or carbon atoms and 1 to 2 hetero atoms, which may be substituted; R⁵ and R⁶ may be the same or different and each represents a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group or a substituted or
55

unsubstituted aralkyl group or an alkoxycarbonyl group, in which R^5 and R^6 may be linked to each other to form a three to seven-membered ring structure comprising carbon atoms and 1 to 2 nitrogen atoms, which may be substituted; X^- represents a pharmaceutically acceptable anion; and m and n may be the same or different and each is an integer of 1 to 3.

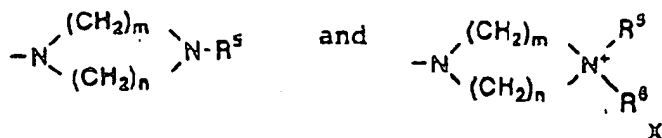
- 5 Further, the present invention provides a 5-HT₃receptor antagonist which comprises the compound represented by the above formula (1) or (2) as an active ingredient and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

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According to the present invention, the alkyl moiety of lower alkyl and lower alkoxy groups may preferably be a straight or branched-chain C_{1-6} alkyl group, and the lower alkenyl group may preferably be a straight or branched-chain C_{2-6} alkenyl group. The aralkyl group contains 7 to 10 carbon atoms. Illustrative examples of substituent groups include a halogen atom and hydroxyl, cyano, acyl, alkoxy, 15 carboxyl, alkoxycarbonyl, carbamoyl, amino, nitro and the like groups. Examples of halogen atoms include fluorine, chlorine, bromine, and iodine. The alkyl moiety of the acyl, alkoxy and alkoxycarbonyl groups contain 1 to 6 carbon atoms. The three to seven-membered ring composed of any two of R^1 to R^4 may include nitrogen, oxygen or sulfur as a hetero atom. Examples of the ring include benzene ring, cyclohexane ring, pyridine ring, piperidine ring, pyrrolidine ring and the like. Examples of the three to 20 seven-membered ring composed of R^5 and R^6 include aziridine ring, pyrrolidine ring, piperidine ring, homopiperidine ring and the like. The pharmaceutically acceptable anion includes halogen ion, sulfate anion, phosphate anion or organic acid anion such as acetate or formate anion. The methylene group of the moiety of

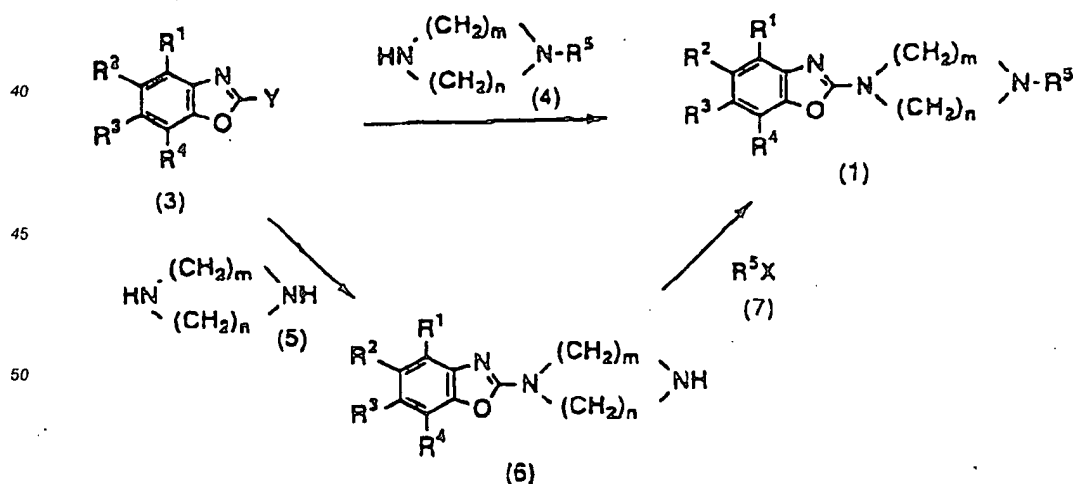
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may be substituted with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, nitro, amino, C_{1-6} alkoxy, carboxyl, hydroxyl, carbamoyl and the like groups.

- 35 The compound of formula (1) of the present invention can be produced by various methods, but preferably by the following two typical methods.



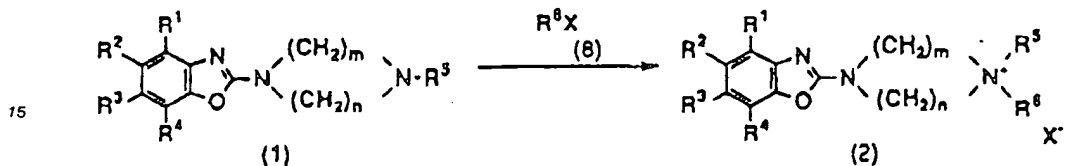
A compound of interest represented by the formula (1), in which $R^1, R^2, R^3, R^4, R^5, m$ and n are defined above, can be obtained by allowing a compound represented by the formula (3), in which R^1, R^2, R^3 and R^4 are defined above and Y represents a halogen atom, to react with an N-substituted alicyclic diamine

represented by the formula (4), in which R^5 , m and n are defined above.

Alternatively, a compound of interest represented by the formula (1), in which R^1 , R^2 , R^3 , R^4 , R^5 , m and n are defined above, can be obtained by allowing a compound represented by the formula (3), in which R^1 , R^2 , R^3 and R^4 are defined above and Y represents a halogen atom, to react with an alicyclic diamine represented by the formula (5), in which m and n are defined above, thereby obtaining a compound represented by the formula (6), in which R^1 , R^2 , R^3 and R^4 are defined above, and subsequently allowing the compound (6) to react with a compound represented by the formula (7), in which R^5 is defined above and X represents a halogen atom.

The compound represented by the formula (2) can be produced by the following method.

10



20 A compound of interest represented by the formula (2) can be obtained by allowing a compound represented by the formula (1), in which R^1 , R^2 , R^3 , R^4 , R^5 , m and n are defined above, to react with a compound represented by the formula (8), in which R^6 is defined above and X represents a halogen atom.

Reaction of the compound (3) with the compound (4) or (5) progresses quickly when the reaction is carried out at a temperature of from 0 to 150°C without using solvents or in a solvent such as dimethylformamide (DMF) or the like. The reaction can be carried out in the presence of a base if necessary.

25 The compound (1) can be obtained easily by carrying out reaction of the compound (6) with the compound (7) at a temperature of from 0 to 80°C for 1 hour to 5 days in a solvent such as DMF or the like. The compound (2) can be obtained from the compounds (1) and (8) in the same manner.

The thus obtained compound can be isolated and purified by conventional methods including recrystallization or chromatography.

30 The compound of the present invention may be formulated into a pharmaceutical composition together with known pharmaceutically acceptable carriers. These compositions may be orally or parenterally administered. Examples of oral dosage forms include tablets, capsules, granules, powders and the like. In the case of parenteral administration, the compound may be formulated into a solution, a suspension and the like and administered intravenously, subcutaneously or intramuscularly.

The composition of the present invention may be given to an adult in a dose of 0.01 to 5 mg/kg/day in terms of the active ingredient by injection, intravenous drip or oral administration.

35 The following examples are provided to further illustrate the present invention. It is to be understood, however, that the examples are for purpose of illustration only and are not to be construed to limit the scope of the present invention, and various alterations and modifications can be made within the scope of the present invention. In the following examples, NMR data are shown as δ values measured by 300 MHz NMR using TMS as the standard.

EXAMPLE 1

45

2-(4-Methyl-1-piperaziny)benzoxazole

To 3.08 g of 2-chlorobenzoxazole was added 200 ml of N-methylpiperazine under cooling with ice, followed by 2 hours of reaction at the same temperature. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 200 ml of ethyl acetate, washed with water, dehydrated with $MgSO_4$ and then concentrated to dryness under a reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 20:1) to obtain 2.77 g of the title compound.

NMR ($CDCl_3$) δ : 7.37 (1H, d), 7.26 (1H, d), 7.18 (1H, t), 7.02 (1H, t), 3.73 (4H, t), 2.54 (4H, t), 2.37 (3H, s)

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EXAMPLE 21,1-Dimethyl-4-(benzoxazol-2-yl)piperazinium iodide

5 A 435 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 6 ml of DMF. Under cooling with ice, 0.19 ml of methyl iodide was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 1 hour at room temperature. The reaction solution was concentrated under a reduced pressure, and 4 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to
 10 obtain 670 mg of the title compound.
 NMR (DMSO-d₆) δ: 7.48 (1H, d), 7.37 (1H, d), 7.22 (1H, t), 7.10 (1H, t), 3.99 (4H, t), 3.58 (4H, t), 3.23 (6H, s)

EXAMPLE 3

15 1-Allyl-1-methyl-4-(benzoxazol-2-yl)piperazinium iodide

A 1.09 g portion of 2-(4-methyl-1-piperazinyl)benzoxazole and 0.69 ml of allyl iodide were treated in the same manner as in Example 2 to obtain 1.88 g of the title compound.
 20 NMR (DMSO-d₆) δ: 7.48 (1H, d), 7.38 (1H, d), 7.21 (1H, t), 7.10 (1H, t), 6.10 (1H, m), 5.71 (2H, dd), 4.18 (2H, d), 4.15 - 3.9 (4H, m), 3.56 (4H, t), 3.15 (3H, s)

EXAMPLE 4

25 1-Allyl-1-methyl-4-(benzoxazol-2-yl)piperazinium chloride

Using 435 mg of 2-(4-methyl-1-piperazinyl)benzoxazole and 0.24 ml of allyl chloride, the same treatment of Example 2 was conducted to obtain 504 mg of the title compound.
 30 NMR (CD₃OD) δ: 7.39 (1H, d), 7.37 (1H, d), 7.23 (1H, t), 7.14 (1H, t), 6.20 - 6.10 (1H, m), 5.82 - 5.78 (2H, m), 4.20 - 4.17 (4H, m), 4.04 - 3.96 (2H, m), 3.70 - 3.60 (4H, m), 3.24 (3H, s)

EXAMPLE 5

35 1-(2-Hydroxyethyl)-1-methyl-4-(benzoxazol-2-yl)piperazinium iodide

A 435 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 3 ml of DMF. Under cooling with ice, 0.24 ml of 2-iodoethyl alcohol was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 17 hours at room temperature, followed by further addition of 0.48 ml 2-iodoethyl alcohol and subsequent 21 hours of reaction at 50 °C. The reaction
 40 mixture was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 583 mg of the title compound.
 NMR (CD₃OD) δ: 7.40 (1H, d), 7.35 (1H, d), 7.21 (1H, t), 7.12 (1H, t), 4.15 - 4.05 (6H, m), 3.88 - 3.80 (2H, m), 3.80 - 3.70 (4H, m), 3.42 (3H, s)

EXAMPLE 6

45 1-Benzyl-1-methyl-4-(benzoxazol-2-yl)piperazinium bromide

50 A 300 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 5 ml of THF. Under cooling with ice, 354 mg of benzyl bromide was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 22 hours at room temperature. The thus formed precipitate was collected by filtration and washed with acetone. The filtrate was concentrated under a reduced pressure, and the resulting residue was dissolved in 50 ml of water, washed with ethyl acetate and
 55 then lyophilized to obtain 496 mg of the title compound.
 NMR (CD₃OD) δ: 7.90 (1H, s), 7.63 - 7.56 (4H, m), 7.40 (1H, d), 7.36 (1H, d), 7.23 (1H, t), 7.13 (1H, t), 4.74 (2H, s), 4.29 (2H, brd), 3.98 - 3.92 (2H, m), 3.77 - 3.72 (2H, m), 3.60 (2H, brd), 3.17 (3H, s)

EXAMPLE 71-Cyanomethyl-1-methyl-4-(benzoxazol-2-yl)piperazinium bromide

- 5 A 150 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 3 ml of DMF. Under cooling with ice, 0.052 ml of bromoacetonitrile was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 24 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then
- 10 dried to obtain 228 mg of the title compound.
NMR (CD₃OD) δ : 7.40 (1H, d), 7.37 (1H, d), 7.23 (1H, t), 7.14 (1H, t), 5.06 (2H, s), 4.27 - 4.21 (2H, m), 4.10 - 4.03 (2H, m), 3.93 - 3.83 (4H, m), 3.52 (3H, s)

EXAMPLE 8

- 15 1-Ethoxycarbonylmethyl-1-methyl-4-(benzoxazol-2-yl)piperazinium bromide

- A 110 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 3 ml of DMF. Under cooling with ice, 101 mg of bromoethyl acetate was added to the thus prepared solution, and the reaction
- 20 was carried out for 1 hour at the same temperature and then for 84 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 167 mg of the title compound.
NMR (CD₃OD) δ : 7.41 (1H, d), 7.38 (1H, d), 7.25 (1H, t), 7.15 (1H, t), 4.60 (2H, s), 4.36 (2H, q), 4.20 - 4.05
- 25 (4H, m), 3.99 - 3.88 (4H, m), 3.52 (3H, s), 1.36 (3H, t)

EXAMPLE 9

- 30 1-Acetonil-1-methyl-4-(benzoxazol-2-yl)piperazinium bromide

- A 100 mg portion of 2-(4-methyl-1-piperazinyl)benzoxazole was dissolved in 3 ml of DMF. Under cooling with ice, 95 mg of bromoacetone was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 60 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting
- 35 residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 119 mg of the title compound.
NMR (CD₃OD) δ : 7.39 (1H, d), 7.36 (1H, d), 7.22 (1H, t), 7.13 (1H, t), 4.81 (2H, s), 4.15 - 4.05 (4H, m), 3.97 - 3.80 (4H, m), 3.47 (3H, s), 2.27 (3H, s)

- 40 EXAMPLE 10

8-(Benzoxazol-2-yl)-8-aza-5-azoniaspiro[4,5]decane iodide

- A 3.07 g portion of 2-chlorobenzoxazole was dissolved in 10 ml of dichloromethane. Under cooling with
- 45 ice, to this was added dropwise 3.45 g of anhydrous piperazine which has been dissolved in 30 ml of dichloromethane, followed by 1 hour of reaction. The reaction solution was concentrated under a reduced pressure, and the resulting residue was purified by a silica gel column chromatography (dichloromethane:methanol = 20:1), followed by concentration of the eluate under a reduced pressure. Thereafter, the resulting residue was dissolved in 30 ml of water, neutralized with 1 N hydrochloric acid, extracted
- 50 with dichloromethane, washed with water, dehydrated with Na₂SO₄ and then concentrated under a reduced pressure to obtain 1.77 g of 2-(1-piperazinyl)benzoxazole.

- A 245 mg portion of potassium carbonate was added to 300 mg of 2-(1-piperazinyl)benzoxazole which had been dissolved in 5 ml of DMF, and the reaction was carried out for 30 minutes. Under cooling with ice, 0.23 ml of 1,4-diiodobutane was added to the resulting solution, and the reaction was carried out for 1 hour
- 55 at the same temperature and then for 2 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and the resulting residue was dissolved in 300 ml of dichloromethane and extracted three times with 100 ml of water. Thereafter, the aqueous layers were combined and lyophilized. By purifying the residue by Diaion HP-20 (Mitsubishi Chemicals), 175 mg of the title compound was

obtained.

NMR (CD₃OD) δ : 7.39 (1H, d), 7.36 (1H, d), 7.23 (1H, t), 7.12 (1H, t), 4.06 (4H, brs), 3.75 (4H, t), 3.70 (4H, t), 2.28 (4H, brs)

5 EXAMPLE 11

2-[4-(2-Hydroxyethyl)-1-piperazinyl]benzoxazole

A 300 mg portion of 2-chlorobenzoxazole was dissolved in 2 ml of DMF. Under cooling with ice, 279 mg of 1-(2-hydroxyethyl)piperazine was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 24 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of ethyl acetate and washed with sodium hydrogencarbonate aqueous solution (pH 8) and then with water. The resulting organic layer was dehydrated with sodium sulfate and concentrated under a reduced pressure to obtain 140 mg of the title compound.

NMR (CD₃OD) δ : 7.31 (1H, d), 7.28 (1H, d), 7.17 (1H, t), 7.05 (1H, t), 3.72 - 3.68 (6H, m), 2.65 (4H, t), 2.58 (2H, t)

20 EXAMPLE 12

1,1-[Di(2-hydroxyethyl)-4-(benzoxazol-2-yl)]piperazinium iodide

A 100 mg portion of 2-[4-(2-hydroxyethyl)-1-piperazinyl]benzoxazole was dissolved in 5 ml of DMF. A 105 mg portion of 2-iodoethyl alcohol was added to the thus prepared solution, and the reaction was carried out for 48 hours at 60°C and then for 5 hours at 90°C. The reaction mixture was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 80 mg of the title compound.

NMR (CD₃OD) δ : 7.39 (1H, d), 7.35 (1H, d), 7.23 (1H, t), 7.13 (1H, t), 4.11 - 4.08 (8H, m), 3.89 - 3.85 (8H, m)

30 EXAMPLE 13

2-(4-Methyl-1-homopiperazinyl)benzoxazole

A 1.54 g portion of 2-chlorobenzoxazole was dissolved in 5 ml of dichloromethane. Under cooling with ice, to this was added dropwise 2.28 g of N-methylhomopiperazine which had been dissolved in 10 ml of dichloromethane, followed by 1 hour of reaction. The reaction solution was concentrated under a reduced pressure, and the resulting residue was dissolved in 500 ml of dichloromethane, washed with water, dehydrated with sodium sulfate and then concentrated under a reduced pressure. Thereafter, the resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 10:1) to obtain 1.87 g of the title compound.

NMR (CD₃OD) δ : 7.30 (1H, d), 7.26 (1H, d), 7.16 (1H, t), 7.02 (1H, t), 3.83 - 3.76 (4H, m), 2.81 - 2.78 (2H, m), 2.67 - 2.65 (2H, m), 2.39 (3H, s), 2.07 - 2.00 (2H, m)

45 EXAMPLE 14

1,1-Dimethyl-4-(benzoxazol-2-yl)homopiperazinium iodide

A 200 mg portion of 2-(4-methyl-1-homopiperazinyl)benzoxazole was dissolved in 5 ml of tetrahydrofuran (THF). Under cooling with ice, 0.064 ml of methyl iodide was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 2 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 320 mg of the title compound.

NMR (CD₃OD) δ : 7.36 (1H, d), 7.31 (1H, d), 7.20 (1H, t), 7.08 (1H, t), 4.13 - 4.12 (2H, m), 3.92 - 3.85 (2H, m), 3.78 - 3.75 (2H, m), 3.70 - 3.67 (2H, m), 3.31 (3H, s), 3.30 (3H, s), 2.38 (2H, brs)

EXAMPLE 151-Allyl-1-methyl-4-(benzoxazol-2-yl)homopiperazinium iodide

5 A 540 mg portion of 2-(4-methyl-1-homopiperazinyl)benzoxazole was dissolved in 5 ml of dichloromethane. Under cooling with ice, 0.32 ml of allyl iodide was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 1 hour at room temperature. The reaction solution was concentrated under a reduced pressure, and 5 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then
 10 dried to obtain 821 mg of the title compound.
 NMR (CD₃OD) δ : 7.36 (1H, d), 7.31 (1H, d), 7.20 (1H, t), 7.08 (1H, t), 6.19 - 6.09 (1H, m), 5.80 - 5.75 (2H, m), 4.22 - 4.12 (4H, m), 3.91 (2H, t), 3.78 - 3.74 (2H, m), 3.70 - 3.67 (2H, m), 3.19 (3H, s), 2.41 (2H, brs)

EXAMPLE 16

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1-(2-Hydroxyethyl)-1-methyl-4-(benzoxazol-2-yl)homopiperazinium iodide

A 100 mg portion of 2-(4-methyl-1-homopiperazinyl)benzoxazole was dissolved in 3 ml of THF. Under cooling with ice, 89 mg of 2-iodoethyl alcohol was added to the thus prepared solution, and the reaction
 20 was carried out for 1 hour at the same temperature and then for 29 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and 3 ml of acetone was added to the resulting residue. The precipitate thus formed was collected by filtration, washed with acetone and then dried to obtain 143 mg of the title compound.
 NMR (CD₃OD) δ : 7.36 (1H, d), 7.31 (1H, d), 7.20 (1H, t), 7.08 (1H, t), 4.16 - 3.64 (12H, m), 3.31 (3H, s), 2.39
 25 (2H, brs)

EXAMPLE 172-(1-Homopiperazinyl)benzoxazole

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A 978 mg portion of homopiperazine was dissolved in 3 ml of DMF. Under cooling with ice, 500 mg of 2-chlorobenzoxazole was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature and then for 24 hours at room temperature. The reaction solution was concentrated under a reduced pressure, and the resulting residue was dissolved in 200 ml of ethyl acetate, washed with
 35 sodium hydrogencarbonate aqueous solution (pH 8) and water in that order, dehydrated with sodium sulfate and then concentrated under a reduced pressure. Thereafter, the resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 10:1) to obtain 540 mg of the title compound.
 NMR (CD₃OD) δ : 7.30 (1H, d), 7.26 (1H, d), 7.16 (1H, t), 7.02 (1H, t), 3.82 - 3.76 (4H, m), 3.06 - 3.03 (2H, m), 2.90 - 2.87 (2H, m), 1.99 - 1.93 (2H, m)

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EXAMPLE 188-(Benzoxazol-2-yl)-8-aza-5-azoniaspiro[4,6]undecane iodide

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A 348 mg portion of 2-(1-homopiperazinyl)benzoxazole was dissolved in 5 ml of DMF, and 221 mg of potassium carbonate was added to the solution, followed by 10 minutes of reaction. Under cooling with ice, 0.253 ml of 1,4-diiodobutane was added to the resulting solution, and the reaction was carried out for 1 hour at the same temperature and then for 24 hours at room temperature, followed by the addition of 221 mg potassium carbonate and subsequent 15 hours of reaction at 70 °C. The reaction solution was concentrated
 50 under a reduced pressure, and the resulting residue was dissolved in 100 ml of dichloromethane and extracted twice with 100 ml of water. The resulting organic layers were combined and lyophilized, and the thus dried residue was purified by Diaion HP-20 (Mitsubishi Chemicals) to obtain 330 mg of the title compound.
 NMR (CD₃OD) δ : 7.36 (1H, d), 7.31 (1H, d), 7.20 (1H, t), 7.08 (1H, t), 4.13 (2H, brs), 3.90 (2H, t), 3.76 - 3.60
 55 (8H, m), 2.39 (2H, brs), 2.25 (4H, brs)

EXAMPLE 192-[4-(2-Hydroxyethyl)-1-homopiperazinyl]benzoxazole

5 A 2.329 g portion of homopiperazine dissolved in 10 ml of THF was mixed with 830 mg of iodoethyl alcohol to carry out 24 hours of reaction at room temperature. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was purified by Sephadex LH-20 (Pharmacia) (chloroform:methanol = 1:1) and Diaion HP-20 (Mitsubishi Chemicals) to obtain 305 mg of 1-(2-hydroxyethyl)-homopiperazine. Next, Under cooling with ice, 150 mg of 1-(2-hydroxyethyl)homopiperazine and 159 mg of 2-chlorobenzoxazole were added to 3 ml of DMF, and the reaction was carried out for 17 hours at the same temperature and then for 24 hours at room temperature. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of ethyl acetate, washed with sodium hydrogencarbonate aqueous solution (pH 8) and water in that order, dehydrated with sodium sulfate and then concentrated under a reduced pressure. Thereafter, the resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 30:1) to obtain 72 mg of the title compound.

15 NMR (CD₃OD) δ : 7.30 (1H, d), 7.27 (1H, d), 7.15 (1H, t), 7.02 (1H, t), 3.81 - 3.75 (4H, m), 3.65 (2H, t), 2.94 - 2.91 (2H, m), 2.78 - 2.67 (8H, m), 2.02 - 1.98 (2H, m)

EXAMPLE 202-(4-Methyl-1-piperazinyl)-6-methoxybenzoxazole

20 A 50 mg portion of 2-hydroxy-4-methoxyaniline hydrochloride dissolved in 15 ml of ethanol was mixed with 16 mg of potassium hydroxide. After 10 minutes of reaction, to this was added 50 ml of carbon disulfide to carry out 24 hours of heating under reflux. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of dichloromethane, washed with water, dehydrated with magnesium sulfate and then concentrated under a reduced pressure. The resulting residue was purified by a silica gel column chromatography (dichloromethane:methanol = 30:1) to obtain 46 mg of 6-methoxy-2-mercaptobenzoxazole.

30 A 100 mg portion of 6-methoxy-2-mercaptobenzoxazole and 172 mg of phosphorus pentachloride were dissolved in 35 ml of chlorobenzene to carry out 8 hours of heating under reflux. The reaction solution was poured into 300 ml of ice water and extracted three times with 100 ml of dichloromethane. The resulting organic layers were combined, dehydrated with sodium sulfate, concentrated under a reduced pressure and then purified by a silica gel column chromatography (n-hexane:chloroform = 1:1), to obtain 79 mg of 2-chloro-6-methoxybenzoxazole.

35 A 60 mg portion of 2-chloro-6-methoxybenzoxazole was dissolved in 20 ml of dichloromethane, and the reaction was carried out for 1 hour under cooling with ice and then for 72 hours at room temperature. To this was added 20 ml of THF to carry out 24 hours of heating under reflux. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of dichloromethane, washed with water, dehydrated with sodium sulfate and then concentrated under a reduced pressure. The resulting residue was purified by a silica gel column chromatography (n-hexane:chloroform = 1:1 and chloroform:methanol = 10:1) to obtain 51 mg of the title compound.

40 NMR (CD₃OD) δ : 7.17 (1H, d), 6.98 (1H, d), 6.80, 6.78 (1H, dd), 3.79 (3H, s), 3.65 (4H, t), 2.56 (4H, t), 2.35 (3H, s)

EXAMPLE 211-Allyl-1-methyl-4-(6-methoxybenzoxazol-2-yl)piperazinium iodide

50 A 50 mg portion of 2-(4-methyl-1-piperazinyl)-6-methoxybenzoxazole was dissolved in 5 ml of THF. Under cooling with ice, 0.03 ml of allyl iodide was added to the thus prepared solution, and the reaction was carried out for 1 hour at the same temperature followed by reflux for 16 hours under heating. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of ethyl acetate, extracted twice with 100 ml of water and then lyophilized to obtain 73 mg of the title compound.

55 NMR (CD₃OD) δ : 7.24 (1H, d), 7.05 (1H, d), 6.85, 6.83 (1H, dd), 6.18 - 6.10 (1H, m), 5.82 - 5.78 (2H, m), 4.19 (2H, d), 4.15 - 4.11 (2H, m), 4.00 - 3.90 (2H, m), 3.81 (3H, s), 3.70 - 3.61 (4H, m), 3.24 (3H, s)

EXAMPLE 221-Allyl-1-methyl-4-(6-hydroxybenzoxazol-2-yl)piperazinium iodide

5 In an atmosphere of argon gas, 150 mg of 2-chloro-6-methoxybenzoxazole dissolved in 30 ml of dichloromethane was mixed with 8.7 ml of 1.0 M BBr_3 dichloromethane solution and refluxed under heating for 4 hours. The reaction mixture was poured into ice water and extracted three times with 30 ml of dichloromethane. Thereafter, the resulting dichloromethane layers were combined, dehydrated with sodium sulfate and then concentrated under a reduced pressure.

10 Next, the resulting residue was dissolved in 3 ml of THF and, under cooling with ice, mixed with 81 mg of N-methylpiperazine to carry out 30 minutes of reaction at the same temperature. After 2 hours of heating under reflux, the resulting reaction mixture was mixed with 100 ml of chloroform and washed with water, and the water layer was neutralized and extracted with 50 ml of chloroform. The resulting chloroform layers were combined, dehydrated with sodium sulfate and then concentrated under a reduced pressure.

15 Next, the resulting residue was dissolved in 3 ml of THF and, under cooling with ice, mixed with 0.055 ml of allyl iodide to carry out the reaction for 1 hour at the same temperature and then for 19 hours at room temperature. To this was added 0.11 ml of allyl iodide to carry out 30 minutes of reflux under heating. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 50 ml of water and washed with ethyl acetate. Thereafter, the resulting water layer was lyophilized and purified
20 by Sephadex LH-20 (Pharmacia) (chloroform:methanol = 1:1) to obtain 72 mg of the title compound.
NMR (CD_3OD) δ : 7.16 (1H, d), 6.85 (1H, d), 6.72, 6.70 (1H, dd), 6.19 - 6.11 (1H, m), 5.83 - 5.78 (2H, m), 4.19 (2H, d), 4.16 - 4.09 (2H, m), 4.00 - 3.90 (2H, m), 3.75 - 3.57 (4H, m), 3.23 (3H, s)

EXAMPLE 23

25 2-(4-Methyl-1-piperazinyl)-6-nitrobenzoxazole

A 500 mg portion of 2-amino-5-nitrophenol dissolved in 35 ml of ethanol was mixed with 180 mg of potassium hydroxide. After 10 minutes of reaction, the resulting solution was mixed with 35 ml of carbon
30 disulfide and refluxed under heating for 48 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residue was dissolved in 300 ml of ethyl acetate and washed with an aqueous acidic solution of hydrochloric acid (pH 4) and water in that order. The resulting ethyl acetate layers were combined, dehydrated with sodium sulfate and then concentrated under a reduced pressure. Thereafter, the resulting residue was purified by a silica gel column chromatography (chloroform) to obtain 629 mg of 2-
35 mercapto-6-nitrobenzoxazole.

A 200 mg portion of 2-mercapto-6-nitrobenzoxazole dissolved in 40 ml of anhydrous benzene was mixed with 680 mg of phosphorus pentachloride, and the mixture was refluxed under heating for 48 hours. Under cooling with ice, 2.04 g of N-methylpiperazine dissolved in 5 ml of anhydrous benzene was added to the resulting solution, and the reaction was carried out for 2 hours at the same temperature. After adding
40 the same amount of N-methylpiperazine, the reaction was continued for additional 72 hours at room temperature. Precipitated materials in the reaction solution were removed by filtration, and the resulting filtrate was concentrated under a reduced pressure. The thus obtained residue was dissolved in 300 ml of ethyl acetate, washed three times with water, dehydrated with sodium sulfate and then concentrated under a reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 15:1) to obtain 230 mg of the title compound.
45 NMR (CD_3OD) δ : 8.20 - 8.16 (2H, m), 7.32 (1H, d), 3.80 - 3.78 (4H, m), 2.61 - 2.58 (4H, m), 2.37 (3H, s)

EXAMPLE 24

50 1-Allyl-1-methyl-4-(6-nitrobenzoxazol-2-yl)piperazinium iodide

Under cooling with ice, 50 mg of 2-(4-methyl-1-piperazinyl)-6-nitrobenzoxazole dissolved in 5 ml of DMF was mixed with 0.021 ml of allyl iodide, and the reaction was carried out for 1 hour at the same temperature and then for 19 hours at room temperature. The reaction mixture was concentrated under a
55 reduced pressure, and the resulting residue was purified by Sephadex LH-20 (Pharmacia) (chloroform:methanol = 1:1) to obtain 67 mg of the title compound.
NMR (CD_3OD) δ : 8.24 (1H, d), 8.20, 8.18 (1H, dd), 7.40 (1H, d), 6.23 - 6.13 (1H, m), 5.87 - 5.79 (2H, m), 4.31 - 4.26 (4H, m), 4.15 - 4.08 (2H, m), 3.80 - 3.69 (4H, m), 3.29 (3H, s)

EXAMPLE 252-(4-Methyl-1-piperazinyl)naphtho[2,3-d]oxazole

5 A 500 mg portion of 3-amino-2-naphthol dissolved in 100 ml of ethanol was mixed with 193 mg of potassium hydroxide. After 10 minutes of reaction, the resulting solution was mixed with 50 ml of carbon disulfide and refluxed under heating for 10 hours. The reaction solution was concentrated under a reduced pressure, and the resulting residue was dissolved in 100 ml of ethyl acetate, washed with water, dehydrated with sodium sulfate and then concentrated under a reduced pressure. Thereafter, the resulting residue was
 10 purified by a silica gel column chromatography (n-hexane:ethyl acetate = 2:1) to obtain 600 mg of 2-mercaptanaphtho[2,3-d]benzoxazole.

A 100 mg portion of 2-mercaptanaphtho[2,3-d]oxazole dissolved in 30 ml of anhydrous benzene was mixed with 130 mg of phosphorus pentachloride, and the mixture was refluxed under heating for 2 hours. To this was further added 90 mg of phosphorus pentachloride, followed by additional 2.5 hours of heating
 15 under reflux. Under cooling with ice, 995 mg of N-methylpiperazine was added to the resulting solution, and the reaction was carried out for 1 hour at the same temperature and then for 48 hours at room temperature. Precipitated materials in the reaction solution were removed by filtration, and the resulting filtrate was concentrated under a reduced pressure. The thus obtained residue was dissolved in 300 ml of ethyl acetate, washed three times with water, dehydrated with sodium sulfate and then concentrated under a
 20 reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol = 50:1) to obtain 18 mg of the title compound.

NMR (CD₃OD) δ : 7.85 - 7.82 (2H, m), 7.68 (1H, d), 7.61 (1H, s), 7.40 - 7.33 (2H, m), 3.76 (4H, t), 2.58 (4H, t), 2.36 (3H, s)

25 EXAMPLE 261-Allyl-1-methyl-4-(naphtho[2,3-d]oxazol-2-yl)piperazinium iodide

Under cooling with ice, 18 mg of 2-(4-methyl-1-piperazinyl)naphtho[2,3-d]oxazole dissolved in 5 ml of
 30 DMF was mixed with 14 mg of allyl iodide, and the reaction was carried out for 1 hour at the same temperature and then for 1.5 hours at room temperature. The reaction mixture was concentrated under a reduced pressure, and 10 ml of ethyl acetate was added to the resulting residue. Thereafter, the precipitate thus formed was collected by filtration, dissolved in 5 ml of water and then lyophilized to obtain 28 mg of the title compound.

35 NMR (CD₃OD) δ : 7.90 - 7.88 (2H, m), 7.79 (1H, s), 7.72 (1H, s), 7.43 - 7.39 (2H, m), 6.21 - 6.10 (1H, m), 5.83 - 5.79 (2H, m), 4.30 - 4.19 (4H, m), 4.13 - 4.06 (2H, m), 3.75 - 3.64 (4H, m), 3.26 (3H, s)

Next, pharmacological effects of the compounds of the present invention are described in the following test examples.

40 TEST EXAMPLE 15-HT₃ receptor binding affinity

Using a membrane fraction prepared from rat N1E-115 cells in accordance with the procedure of
 45 Lummis *et al.* (*European Journal of Pharmacology*, 189, 223 - 227, 1990), effects of the inventive compounds to inhibit binding of [³H]-GR65630 which was radioligand 5-HT₃ antagonist to 5-HT₃ receptor were examined, with the results shown in Table 1.

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Table 1

5	5-HT ₃ receptor binding affinity	
	Compound	Binding inhibitory ratio of [³ H]-GR65630 at 10 ⁻⁷ M
	Example 1	89.4%
	Example 2	45.5%
	Example 3	52.8%
10	Example 4	48.0%
	Example 5	78.0%
	Example 13	97.3%
	Example 14	44.4%
	Example 16	46.0%
15	Example 19	54.3%
	Example 22	51.6%

TEST EXAMPLE 2

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5-HT₃ receptor antagonism

In accordance with the procedure of Saxena *et al.* (*Arch. Int. Pharmacodyn.*, 277, 235-252, 1985), each compound was dissolved in distilled water for injection to give different concentration and was administered intraperitoneally to mice which had been anesthetized with pentobarbital (3 animals per group), and ratio of inhibition of bradycardia induced by 5-HT administration (0.25 mg/kg, i.v.) was examined 30 minutes thereafter. The results are shown in Table 2.

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Table 2

35	5-HT ₃ receptor antagonism		
	Compound	Dose (mg/kg)	Inhibitory ratio
	Example 1	3	76%
	Example 3	0.3	82%
	Example 5	0.3	61%

40 TEST EXAMPLE 3

Antiemetic effect in cisplatin-treated dogs

Each of test dogs (2 animals per group) after 16 hours of fasting was fed with 200 g of a solid food, and cisplatin was administered to the animal 30 minutes thereafter by intravenous injection with a dose of 3 mg/kg. The test compound was dissolved in distilled water for injection and was administered by intravenous injection 30 minutes before and 2 hours after the cisplatin administration, and frequency and duration of emesis were observed over 6 hours. The results are shown in Table 3.

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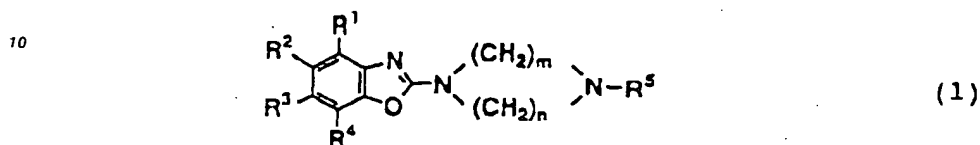
Table 3

55	Antiemetic effect in cisplatin-treated dogs			
	Compound	Dose (mg/kg)	Frequency of emesis (times)	Duration of emesis (hr)
	Control	-	13.5	2.63
	Example 3	0.1 x 2	0	-

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

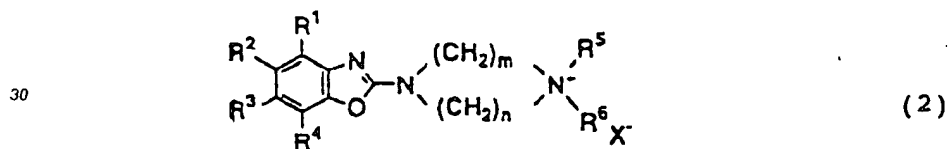
5 Claims

1. A compound represented by the formula (1)



15 wherein R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a halogen atom, a hydroxyl group, an amino group, a lower alkoxy group, a carboxyl group, a carbamoyl group or a nitro group, in which any two groups of R¹ to R⁴ may be linked to each other to form a three
20 to seven-membered ring structure comprising carbon atoms alone or carbon atoms and 1 to 2 hetero atoms, which may be substituted; R⁵ represents a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted aralkyl group or an alkoxycarbonyl group; and m and n may be the same or different and each is an integer of 1 to 3.

- 25 2. A compound represented by the formula (2)



35 wherein R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a halogen atom, a hydroxy group, an amino group, a lower alkoxy group, a carboxyl group, a carbamoyl group or a nitro group, in which any two groups of R¹ to R⁴ may be linked to each other to form a three
40 to seven-membered ring structure comprising carbon atoms alone or carbon atoms and 1 to 2 hetero atoms, may be substituted; R⁵ and R⁶ may be the same or different and each represents a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted aralkyl group or an alkoxycarbonyl group, in which R⁵ and R⁶ may be linked to each other to form a three to seven-membered ring structure comprising carbon atoms and 1 to 2 nitrogen atoms, which may be substituted; X⁻ represents a pharmaceutically acceptable anion; and m and n may be the same or different and each is an integer of 1 to 3.

- 45 3. The compound according to claim 1, wherein said lower alkyl group contains 1 to 6 carbon atoms, said lower alkoxy group contains 1 to 6 carbon atoms, said lower alkenyl group contains 2 to 6 carbon atoms and said aralkyl group contains 7 to 10 carbon atoms.
- 50 4. The compound according to claim 1, wherein said substituted lower alkyl, lower alkenyl, three to seven-membered ring and aralkyl group are substituted with a halogen atom, a hydroxyl group, a cyano group, an acyl group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, an amino group or a nitro group.
- 55 5. The compound according to claim 1, wherein said three to seven-membered ring is selected from the group consisting of benzene, cyclohexane, pyridine, piperidine and pyrrolidine.

6. The compound according to claim 2, wherein said lower alkyl group contains 1 to 6 carbon atoms, said lower alkoxy group contains 1 to 6 carbon atoms, said lower alkenyl group contains 2 to 6 carbon atoms and said aralkyl group contains 7 to 10 carbon atoms.
- 5 7. The compound according to claim 2, wherein said substituted lower alkyl, lower alkenyl, three to seven-membered ring and aralkyl group are substituted with a halogen atom, a hydroxyl group, a cyano group, an acyl group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, an amino group or a nitro group.
- 10 8. The compound according to claim 2, wherein said three to seven-membered ring formed by two groups of R¹ to R⁴ is selected from the group consisting of benzene, cyclohexane, pyridine, piperidine and pyrrolidine.
- 15 9. The compound according to claim 2, wherein said three to seven-membered ring formed by R⁵ and R⁶ is selected from the group consisting of aziridine, pyrrolidine, piperidine and homopiperidine.
10. The compound according to claim 2, wherein said pharmaceutically acceptable anion include halogen ion, sulfate anion, phosphate anion, acetate anion and formate anion.
- 20 11. A serotonin 5-HT₃ receptor antagonist which comprises the compound of claim 1 or 2 as an active ingredient and a pharmaceutically acceptable carrier.
12. The use of the compound of claim 1 or 2 for preparation of a pharmaceutical composition for blocking serotonin 5-HT₃ receptor.

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European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 94 10 5997

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	EP-A-0 398 425 (JANSSEN PHARMACEUTICA N.V.) * claims *	1,3-5	C07D263/58 C07D487/10 A61K31/42 A61K31/495
X	US-A-3 331 843 (ANDREW STEPHEN ET AL) * column 3; claims 1,8 *	1,3-5,12	
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 11, no. 5 , 26 August 1968 , WASHINGTON US pages 1090 - 1092 MATTHEW VERDERAME 'Synthesis of 1,4-disubstituted piperazines' *page 1091,compound 17*	1,3-5,12	
A	EP-A-0 512 939 (FABRICA ESPANOLA DE PRODUCTOS QUIMICOS Y FARMACEUTICOS) * the whole document *	1,2, 10-12	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
			C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 21 June 1994	Examiner Henry, J
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons a : member of the same patent family, corresponding document	